Right and Left Heart Function in Lowlanders with COPD at Altitude: Data from a Randomized Study

Lichtblau, Mona ; Latshang, Tsogyal D ; Furian, Michael ; Müller-Mottet, Séverine ; Küest, Silke ; Tanner, Felix ; Grünig, Ekkehard ; Bloch, Konrad E ; Ulrich, Silvia

Abstract: BACKGROUND Changes in pulmonary hemodynamics and cardiac function in patients with chronic obstructive pulmonary disease (COPD) traveling to altitude have not been assessed despite an increasing prevalence of the disease. OBJECTIVES We hypothesized that pulmonary artery pressure (PAP) significantly increases and cardiac function deteriorates during exposure to hypobaric hypoxia as encountered by traveling to moderate altitude or air flight. METHODS A total of 37 patients (17 female; median age [quartiles] 66 years [60; 69] with COPD GOLD grade 2-3 [FEV1 57% predicted (49; 71)]) living < 800 m underwent echocardiography in Zurich (490 m) and after 1 night at Davos Jakobshorn (2,590 m) in a randomized order of allocation. RESULTS The transtricuspid pressure gradient increased from 23 mm Hg (18; 29) to 32 mm Hg (25; 41) ($p < 0.0001$; Δmedian [95% CI] 7.5 [2.0; 13.0]), the right ventricular fractional area change decreased from 45% (39; 49) to 38% (33; 43) ($p = 0.002$), while the heart rate and systolic blood pressure increased from 70 bpm (64; 78) to 82 bpm (70; 86) ($p < 0.0001$) and from 133 mm Hg (123; 141) to 136 mm Hg (126; 148) ($p = 0.002$), respectively, and left ventricular diastolic dysfunction was more prevalent (24-54%, $p = 0.02$). CONCLUSIONS This is a first study assessing changes in pulmonary hemodynamics and cardiac function in patients with COPD during a short altitude sojourn. Despite the increase in PAP and indications of change in cardiac function, the exposure was well tolerated. None of the patients had to descend to lower altitude for symptomatic altitude-related disease.

DOI: https://doi.org/10.1159/000492898

Originally published at:
Lichtblau, Mona; Latshang, Tsogyal D; Furian, Michael; Müller-Mottet, Séverine; Küest, Silke; Tanner, Felix; Grünig, Ekkehard; Bloch, Konrad E; Ulrich, Silvia (2019). Right and Left Heart Function in Lowlanders with COPD at Altitude: Data from a Randomized Study. Respiration, 97(2):125-134.
DOI: https://doi.org/10.1159/000492898

Clinical Investigations

Respiration

Respiration
DOI: 10.1159/000492898

Received: May 15, 2018
Accepted after revision: August 13, 2018
Published online: September 28, 2018

Right and Left Heart Function in Lowlanders with COPD at Altitude: Data from a Randomized Study

Mona Lichtblau[a] Tsogyal D. Latshang[a] Michael Furian[a]
Séverine Müller-Mottet[a] Silke Küest[b] Felix Tanner[b] Ekkehard Grünig[c]
Konrad E. Bloch[a] Silvia Ulrich[a]

[a]Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland; [b]Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; [c]Thoraxklinik, University Hospital Heidelberg, German Center for Lung Research (DZL), Heidelberg, Germany

Keywords
Altitude · Chronic obstructive pulmonary disease · Echocardiography · Pulmonary hypertension

Abstract
Background: Changes in pulmonary hemodynamics and cardiac function in patients with chronic obstructive pulmonary disease (COPD) traveling to altitude have not been assessed despite an increasing prevalence of the disease. ***Objectives:*** We hypothesized that pulmonary artery pressure (PAP) significantly increases and cardiac function deteriorates during exposure to hypobaric hypoxia as encountered by traveling to moderate altitude or air flight. ***Methods:*** A total of 37 patients (17 female; median age [quartiles] 66 years [60; 69] with COPD GOLD grade 2–3 [FEV_1 57% predicted (49; 71)]) living <800 m underwent echocardiography in Zurich (490 m) and after 1 night at Davos Jakobshorn (2,590 m) in a randomized order of allocation. ***Results:*** The transtricuspid pressure gradient increased from 23 mm Hg (18; 29) to 32 mm Hg (25; 41) ($p < 0.0001$; Δmedian [95% CI] 7.5 [2.0; 13.0]), the right ventricular fractional area change decreased from 45% (39; 49) to 38% (33; 43) ($p = 0.002$), while the heart rate and systolic blood pressure increased from 70 bpm (64; 78) to 82 bpm (70; 86) ($p < 0.0001$) and from 133 mm Hg (123; 141) to 136 mm Hg (126; 148) ($p = 0.002$), respectively, and left ventricular diastolic dysfunction was more prevalent (24–54%, $p = 0.02$). ***Conclusions:*** This is a first study assessing changes in pulmonary hemodynamics and cardiac function in patients with COPD during a short altitude sojourn. Despite the increase in PAP and indications of change in cardiac function, the exposure was well tolerated. None of the patients had to descend to lower altitude for symptomatic altitude-related disease.

Introduction

Despite an increasing prevalence of chronic obstructive pulmonary disease (COPD) in the general population and an increasing number of people traveling to high altitude due to professional and recreational activities, only few studies on COPD patients exposed to hypobaric hypoxia at altitude report about possible implications on

ClinicalTrials.gov registration No. NCT0187513.

KARGER

E-Mail karger@karger.com
www.karger.com/res

Prof. Dr. Silvia Ulrich
Department of Pulmonology, University Hospital Zurich
Rämistrasse 100
CH–8091 Zurich (Switzerland)
E-Mail silvia.ulrich@usz.ch

health and preventive strategies [1–4]. The reported evidence for an altitude-associated increase in mortality rate with COPD underscores the need for research in this field [5, 6]. This is especially true for countries in which part of the population lives at higher altitude.

COPD is the most common chronic respiratory disease worldwide and is characterized by chronic airflow obstruction with airway inflammation, remodeling, and parenchymal destruction of the lung (emphysema) in some patients. Cardinal symptoms of COPD are chronic productive cough and dyspnea on exertion with limited exercise performance related to dynamic hyperinflation, exercise desaturation, and an increase in pulmonary artery pressure (PAP) [7]. Pulmonary hypertension (PH) is a complication in COPD with increasing prevalence with the severity of parenchymal lung destruction due to loss of the pulmonary capillary bed, increased hypoxic pulmonary vasoconstriction [8, 9], and left ventricular (LV) diastolic dysfunction [10]. Exercise-induced PH usually precedes resting PH; a sustained elevation of the mean PAP may ultimately lead to right ventricular (RV) failure and reduced survival rates [11, 12]. The structural and functional alterations of pulmonary vessels in patients with COPD increase the risk of developing symptomatic PH due to excessive hypoxic pulmonary vasoconstriction when traveling to altitude.

To date, the changes in cardiac function in lowlanders with COPD traveling to altitude are still incompletely understood. Therefore, the objective of our study was to perform a detailed echocardiographic and clinical investigation to quantify right and left heart function and hemodynamics in lowlanders with COPD traveling to high altitude.

We hypothesized that PAP would significantly increase and cardiac function deteriorate during exposure to even mild hypobaric hypoxia, similar to what is encountered by many tourists traveling to moderate altitude or by commercial air flight passengers exposed to an altitude equivalent up to 8,000 ft (2,437 m).

Methods

Study Design and Subjects

The current data were collected from participants in a randomized crossover trial evaluating the exercise performance of COPD patients traveling from 490 to 2,590 m (ClinicalTrail.gov Identifier: NCT01875133). In that study [13], clinical characteristics, pulmonary function, and exercise tests were analyzed. The echocardiographic data reported here have not been published yet.

Men and women with moderate-to-severe COPD (GOLD grade 2 or 3) in stable condition living <800 m and aged 18–75 years were included in this study. Patients were excluded if the following criteria were met: hypoxemia at 490 m (PaO_2 <7.3 kPa); unstable condition; COPD exacerbation; uncontrolled cardiovascular disease; use of drugs that affect respiratory center drive; known obstructive sleep apnea syndrome; any other pulmonary disease; internal, neurologic, or psychiatric disease that interferes with protocol compliance, including current heavy smoking (>20 cigarettes per day); previous intolerance to high altitude (<2,600 m); or pregnancy.

Interventions

The patients underwent clinical and echocardiographic assessments at the University Hospital Zurich (490 m, low altitude; baseline) and at the Hotel Davos Jakobshorn, Switzerland (2,590 m) in the afternoon after spending 1 night at altitude. Transfers between locations were made by train and cable car within 2–5 h. The altitude exposure sequence was randomized according to a crossover design and a washout phase between examinations of >2 weeks at 490 m.

Assessments

Patients' medical history was obtained, a clinical examination was performed, and the patients' vital parameters were measured at each altitude. Lung function testing including diffusion capacity was conducted (Bodystik™ and Diffustik™; Geratherm Respiratory GmbH, Bad Kissingen, Germany). Six-minute walking distance was measured according to the guidelines of the American Thoracic Society [14].

Echocardiography

Doppler echocardiographic recordings were obtained with a real-time, phased array sector scanner (CX50 echocardiography unit with S5-1 transducer; Philips, Zofingen, Switzerland) according to guidelines of the European Association of Echocardiography [15–17]. The transtricuspid pressure gradient (TPG) was estimated from the tricuspid regurgitation peak systolic flow velocity obtained with CW Doppler using the modified Bernoulli equation: $\Delta P = 4 \times V_{max}^2$. Right atrial pressure (RAP) was estimated by the respiratory variability in the diameter of the inferior vena cava. The systolic PAP (sPAP) was calculated as the summation of TPG and RAP [17]. Areas of the right atrium and RV were manually traced, and the RV fractional area change (FAC) was calculated. Tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode. The tissue Doppler systolic peak velocity of the RV free wall was assessed. The mean PAP was estimated from the acceleration time (AT) measured with PW Doppler in the RV outflow tract, as described by Kitabatake et al. [18]. To account for the influence of heart rate on AT, it was divided by heart rate.

The pulmonary artery wedge pressure (PAWP) was calculated using the Nagueh formula: $PAWP = 1.24 \times (E/e') + 1.9$ [19]. Diastolic function was graded according to the 2009 EAE/ASE Recommendations using septal e′, lateral e′, left atrial (LA) volume index, and E/A ratio. We considered septal e′ ≥8, lateral e′ ≥10, and LA volume index <34 mL/m^2 to signify normal diastolic function; if those thresholds were not met, diastolic dysfunction was considered and further assessed by E/A ratio and average E/e′ [20].

The imaging sequences were stored and double-checked by an independent echocardiographer (M.L.) blinded to the location. In case of relevant discrepancies in measurements, images were discussed among the echocardiographers – still blinded to location – and chosen upon agreement.

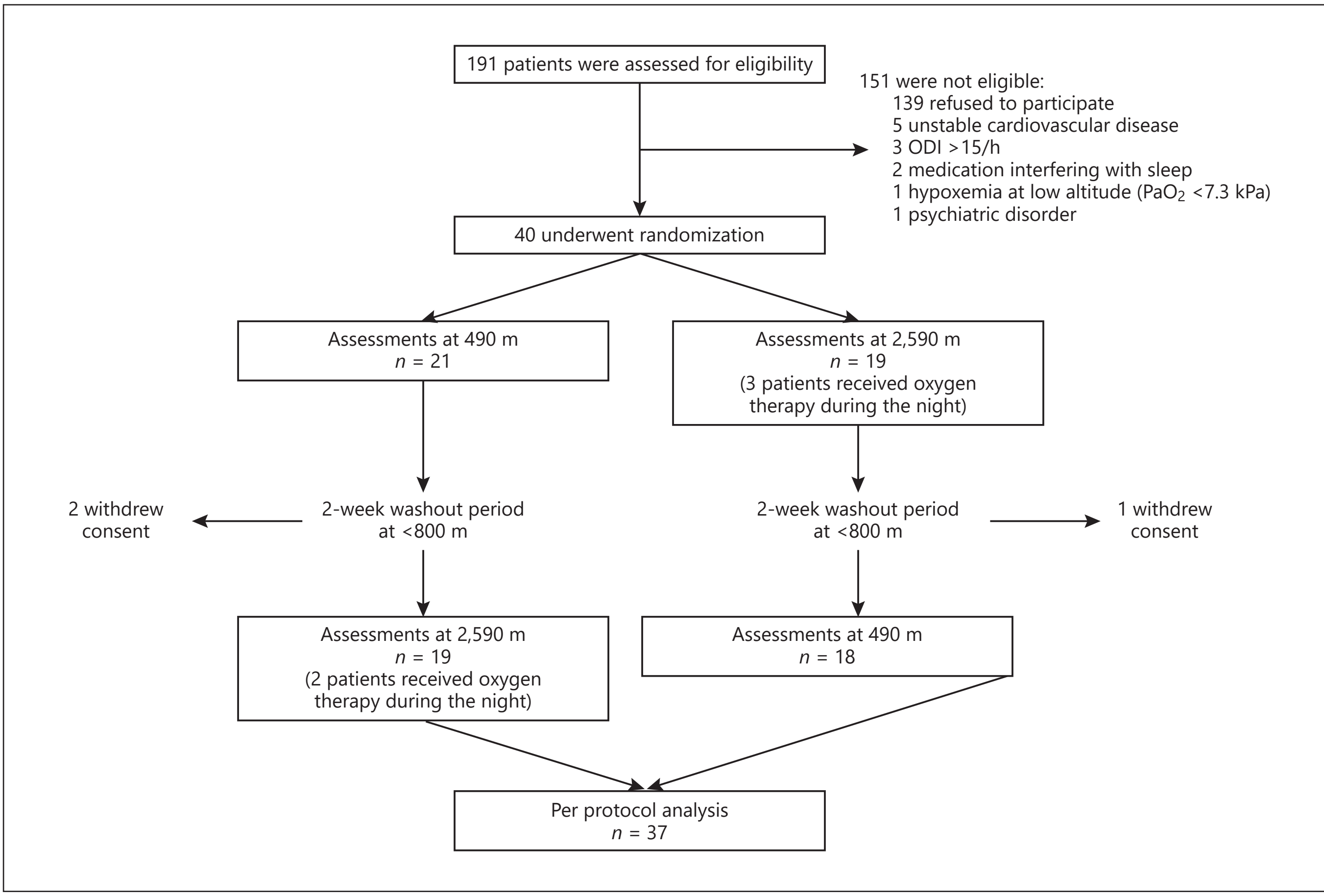

Fig. 1. Flowchart of the study. ODI, oxygen desaturation index.

Data Analysis and Statistics

Data analysis and statistics were performed with SPSS version 22; for regression analysis, STATA version 15 was used. The analysis was performed according to the per protocol principle on participants with data from both study locations. The data are summarized as median (lower and upper quartile) or *n* (%). Effects of altitude were evaluated by Wilcoxon matched-pair tests or χ^2 test and by computing mean differences with 95% CI.

Linear regression analysis was used to assess the potential effects of various baseline characteristics on the TPG at altitude. A probability of $p < 0.05$ was considered statistically significant.

Results

Of 191 screened patients, 151 could not be included for various reasons; 40 fulfilled the inclusion criteria and were randomized, but 3 patients withdrew their consent during the study (Fig. 1). Data about 37 patients were available for the per protocol analysis. Their characteristics are presented in Table 1. Their median age (quartiles) was 66 years (60; 69), 54% of the participants were male, the body mass index was 28.1 (22.1; 30.2), the median FEV_1 was 57% predicted (49; 71), and FEV_1/FVC was 51% (42; 60). Comorbidities included arterial hypertension in 62% and stable cardiovascular diseases in 23% of the patients.

The evaluation at 2,590 m, after the patients had spent 1 night at 2,590 m, revealed a significant decrease in PaO_2 from 9.0 kPa (8.4; 9.4) to 6.6 kPa (6.3; 7.2) along with a reduced SaO_2 from 94% (93; 95) to 87% (84; 91) (both $p < 0.001$). This was generally well tolerated. None of the patients had to descend to lower altitude for symptomatic altitude-related disease; however, 5 patients required supplemental oxygen therapy during the night because of severe nocturnal hypoxemia (defined as SpO_2 <80% for ≥30 min).

Table 1. Patient characteristics

	Zurich (490 m)
Subjects, *n*	37; 20 men (54%)
Age, years	66 (60; 69)
Height, cm	170 (165; 177)
Weight, kg	78 (66; 88)
Body surface area, m^2	1.9 (1.7; 2.0)
Body mass index	28.1 (22.1; 30.2)
PaO_2, kPa	9.0 (8.3; 9.4)
SaO_2, %	94 (93; 95)
GOLD grade 2/3	21/16 (57/43)
Current/ex-/no smoker	8/28/1 (23/76/2)
Pack-years	45 (20; 68)
Lung function testing	
FEV_1, % predicted (after bronchodilation)	57 (49; 71)
FEV_1/FVC ratio	51 (42; 61)
DLCO (Hb), % predicted	58 (49; 68)
Arterial hypertension	23 (62)
Cardiovascular disease (CAD, PAOD, CVI)	8 (23)
Six-min walking distance, m	542 (471; 585)
SpO_2 end 6-min walking distance, %	89 (82; 92)
Inhalation of glucocorticoids	23 (62)
Inhalation of β-mimetics	31 (84)
Inhalation of anticholinergics	30 (81)
Roflumilast	3 (8)
Theophylline	2 (5)
Diuretics	10 (27)
ACE inhibitor or AT2 antagonist	20 (54)
β-Blocker	8 (22)
Calcium channel blocker	6 (16)
Lipid-lowering therapy	7 (19)
Antidiabetics	2 (5)
Antidepressants	7 (19)
Antiplatelet aggregation therapy	7 (19)

Data are displayed as median (quartiles) or *n* (%). PaO_2, oxygen partial pressure in arterial blood; SaO_2, oxygen saturation in arterial blood; SpO_2, oxygen saturation pulse oximetry; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DLCO (Hb), diffusing capacity for carbon monoxide (adjusted for hemoglobin); CAD, coronary artery disease; PAOD, peripheral arterial occlusive disease; CVI, cerebrovascular insult; ACE, angiotensin-converting enzyme.

Right Heart Function and Morphology

The pulmonary hemodynamics and RV function are shown in Table 2. The tricuspid regurgitation peak systolic velocity (TRV) and consecutive TPG showed a significant increase (TRV from 2.4 m/s [2.1; 2.7] to 2.8 m/s [2.5; 3.2], $p < 0.0001$; TPG from 23 mm Hg [18; 29] to 32 mm Hg [25; 41], $p < 0.0001$) (Fig. 2, 3). At low altitude, 6 patients had a TRV >2.8 m/s, and at high altitude this was the case for 18 patients. The RV outflow tract AT increased with altitude, even when indexed for heart rate (Table 2); correspondingly, the mean PAP increased from 19 mm Hg (16; 20) to 28 mm Hg (22; 37) ($p = 0.0001$). The RV end-systolic area increased, while the RV end-diastolic area remained unchanged, resulting in a reduced RV FAC and an increase in RAP. The RV wall thickness, RV/LV ratio, eccentricity indices, septal motion, TAPSE, and tissue Doppler RV systolic excursion velocity s′ remained unchanged.

Left Heart Function and Morphology

All participants had normal LV systolic function at 490 m. With ascent from 490 to 2,590 m, there was a significant increase in heart rate and a slight increase in systemic systolic blood pressure, a small increase in aortic root diameter, and a minor reduction of the LV ejection fraction (LVEF) (Table 3). The mitral E/A ratio, septal mitral annulus e′ wave, and average mitral annulus e′, as well as the septal E/e′ ratio and the lateral and septal e′/a′ ratio, remained unchanged. The percentage of subjects with diastolic dysfunction, which was assessed individually according to the 2009 EAE/ASE guidelines [20], doubled with ascent to 2,590 m (from 24 to 54%, $p = 0.012$). No significant change in LA dimensions and in PAWP occurred (Table 3).

Correlation and Regression Analysis

Multivariate linear regression analysis revealed a weak correlation between baseline TPG and TPG at altitude (Table 4). No other relevant associations between potential clinical characteristics and right or left heart parameters were found in univariate analysis.

Discussion

To our knowledge, the current study is the first comprehensive clinical and echocardiographic evaluation of lowlanders with moderate-to-severe COPD at 2,590 m. The main findings on the day after arrival at the higher altitude consisted of a moderate increase in heart rate and PAP associated with a reduced RV FAC and an increase in RAP. In addition, there was an increase in systemic systolic blood pressure, a minor reduction in LVEF, and an increase in the prevalence of diastolic dysfunction by more than half from 24 to 54% of the participants. These novel findings suggest that the hypoxemia experienced by COPD patients going to an altitude as encountered in many tourist destinations or during commercial air travel is causing considerable impairment of the pulmonary and systemic circulation that may possibly contribute to exercise limitation or even predispose to cardiac failure.

Table 2. Right heart function and morphology ($n = 37$)

Variables	Zurich (490 m)	Jakobshorn (2,590 m)	Median change (95% CI)	p
Tricuspid valve regurgitation peak systolic velocity[a], m/s	2.4 (2.2; 2.7)	2.8 (2.5; 3.2)	0.5 (0.3; 0.6)	<0.0001*
Transtricuspid pressure gradient, mm Hg	23 (19; 29)	32 (25; 41)	7.5 (2.0; 13.0)	0.0001*
Systolic pulmonary artery pressure, mm Hg	28 (24; 35)	39 (34; 49)	8.0 (6.0; 16.6)	<0.0001*
RV outflow tract acceleration time, s	121 (117; 133)	96 (81; 112)	−20 (−40.5; −9)	0.0001*
RV outflow tract acceleration time/heart rate ratio	1.7 (1.5; 2.0)	1.2 (0.9; 1.5)	−0.4 (−0.7; −0.2)	<0.0001*
Mean pulmonary artery pressure, mm Hg	19 (16; 20)	28 (22; 37)	7.1 (3.1; 14.1)	0.0001*
RV end-diastolic area, cm^2	15 (14; 18)	16 (14; 19)	0.4 (−0.9; 1.9)	0.22
RV end-systolic area, cm^2	8 (8; 11)	11 (8; 12)	1.44 (0.4; 2.4)	0.02*
RV fractional area change, %	45 (39; 49)	38 (33; 43)	−7.0 (−10.6; −2.9)	0.002*
RV anterior wall thickness, cm	0.5 (0.4; 0.5)	0.5 (0.4; 0.6)	0.0 (−0.0; 0.1)	0.29
RV/LV ratio	0.4 (0.3; 0.6)	0.4 (0.2; 0.5)	−0.0 (−0.1; 0.0)	0.33
Eccentricity index – diastolic	1.0 (0.9; 1.1)	1.0 (0.9; 1.1)	−0.0 (−0.1; 0.0	0.17
Eccentricity index – systolic	1.0 (0.9; 1.1)	1.0 (1.0; 1.1)	−0.0 (−0.1; 0.2)	0.68
Patients with septal motion deviation	1 (3)	2 (5)		1.0
Tricuspid annular plane systolic excursion, cm	2.3 (2.2; 2.5)	2.3 (2.0; 2.5)	0.0 (−0.2; 0.2)	0.43
RV systolic excursion velocity s′, cm/s	13 (12; 15)	14 (12; 16)	0.6 (−0.7; 1.6)	0.33
Right atrial pressure, mm Hg	5 (5; 5)	5 (5; 10)	0.0 (0.0; 0.0)	<0.001*
Right atrial area, cm^2	13 (12; 17)	13 (12; 17)	−0.6 (−2.4; 0.8)	0.39

Data are displayed as median (quartiles) or *n* (%). RV, right ventricular; LV, left ventricular. * $p < 0.05$. [a] Tricuspid valve regurgitation peak systolic velocity could be obtained from 32 of the 37 patients at 490 m and from 35 of the 37 patients at 2,590 m.

In the literature, many previous studies observing effects of acute exposure to hypobaric or normobaric hypoxia have described increases in PAP in healthy subjects: Kriemler et al. [21] performed an echocardiographic field study on 20 healthy individuals (mean age 44 years) and revealed an increase in mean sPAP from 24 mm Hg at 450 m to 32 mm Hg on the first day at 3,450 m. Similar results from younger study collectives have been reported by several other authors describing sPAP values ranging from 30 ± 6 mm Hg at 3,730 m to 41 ± 3 mm Hg at 5,000 m [22–28]. Thus, with an estimated sPAP of 28 mm Hg (24; 35) at 490 m, the current COPD patients already started with higher pressures at low altitude when compared to healthy subjects, and furthermore showed a greater increase when ascending to 2,590 m; such values were reported for healthy subjects only at very high altitudes (>4,500 m) [22–27].

Even though our COPD patients had values corresponding to those in healthy subjects at very high altitude, they tolerated the exposure to this altitude well, which might be explained by an as yet unknown RV adaptation to hypoxia caused by their underlying pulmonary disease [29]. The higher PAP in COPD patients is most likely due to both restriction of the pulmonary vascular bed due to parenchymal destruction of the lung and a greater degree of hypoxemia with excessive hypoxic pulmonary vasoconstriction. We did not find any significant increase in breath rate or dynamic hyperinflation with altitude in the present COPD cohort [30], and changes in functional residual capacity and the TPG were not correlated. Thus, we do not think that any changes in respiratory mechanics contributed to the increase in PAP in these patients.

In the present study, we did not assess stroke volume and cardiac output, and thus we cannot address potential changes in pulmonary vascular resistance with altitude, which should be included in future research. The higher age of the COPD patients and their impaired LV diastolic function may additionally have contributed. However, only a minority (16%) of the COPD patients in our cohort had a TPG velocity >2.8 m/s, as suggestive of potential PH group 3 in Zürich (460 m), but none had signs of right heart failure.

In the current COPD collective, we found a slightly increased RV end-systolic area and a slightly lower RV FAC at altitude, suggesting mild impairment of RV function probably due to an elevated afterload caused by the increased PAP. These results are in accordance with data published by Güvenç et al. [31] describing larger end-diastolic and end-systolic RV diameters and end-systolic areas as well as reduced FAC in patients with COPD liv-

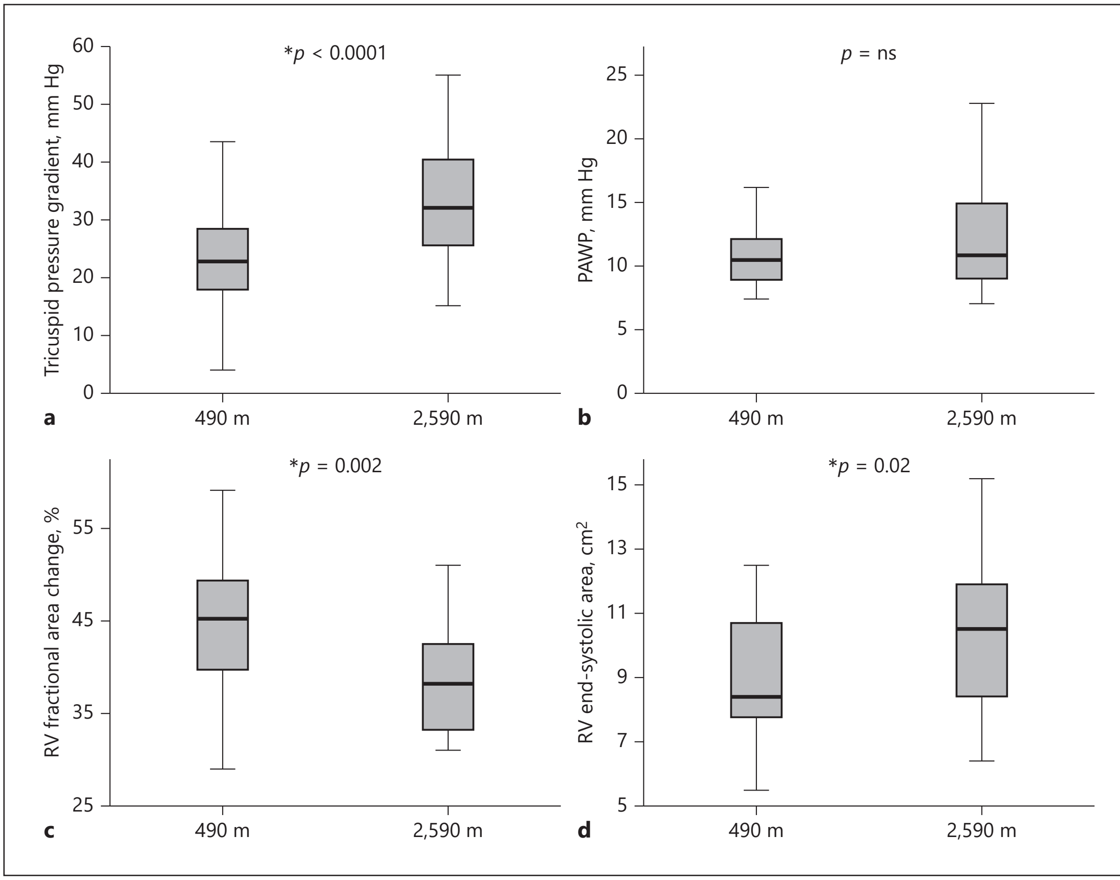

Fig. 2. Transtricuspid pressure gradient (**a**), mean pulmonary artery wedge pressure (PAWP) (**b**), right ventricular (RV) fractional area change (**c**), and RV end-systolic area (**d**) at 490 and 2,590 m are shown. Boxplot horizontal lines represent median values, box borders display quartiles, and upper and lower whiskers display the last value that is in between 1.5× the interquartile range.

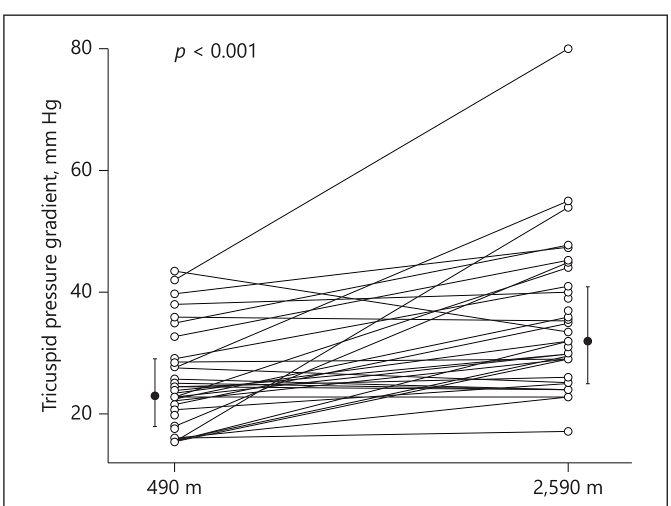

Fig. 3. Individual changes in transtricuspid pressure gradient.

ing at moderate altitude. As in our study collective, Güvenç et al. [31] could not detect any difference in TAPSE when comparing patients with COPD living at sea level with those living at moderate altitude, which might indicate that impairments of RV function are only mild, mainly driven by an increased volume and an only minor reduction in contractility.

The expected increase in heart rate and systemic blood pressure, as known from sojourns to altitude in healthy subjects due to chemoreceptor activation [32], could likewise be observed in this COPD cohort. The systolic LVEF was slightly but significantly reduced at 2,590 m – albeit with a median decrease of only 5%, which should be interpreted with caution, since it could be within the range of measurement variability [33]. In contrast, recent studies have reported an increase in EF with acute exposure to 3,700 m [34] ($n = 139$) and 3,750 m ($n = 15$) in healthy

Table 3. Left heart function and morphology (n = 37)

Variables	Zurich (490 m)	Jakobshorn (2,590 m)	Median change (95% CI)	p
Heart rate, bmp	70 (64; 78)	82 (70; 86)	7 (3; 12)	<0.0001*
Blood pressure – systolic, mm Hg	133 (123; 141)	136 (126; 148)	4.5 (–1.5; 11.5)	0.02*
Blood pressure – diastolic, mm Hg	81 (75; 87)	80 (72; 94)	0.0 (–3.5; 2.0)	0.96
Blood pressure – mean, mm Hg	99 (91; 104)	97 (92; 111)	1.0 (–3.0; 3.5)	0.44
Aortic root diameter, cm	3.2 (2.6; 3.5)	3.5 (3.1; 3.8)	0.2 (0.1; 0.4)	0.0002*
LV ejection fraction (Simpson), %	67 (63; 70)	64 (59; 67)	–4.9 (–6.9; –1.9)	0.04*
Septal wall thickness, cm	0.9 (0.8; 1.1)	1.0 (0.9; 1.1)	0.1 (0.0; 0.2)	0.006*
LV end-diastolic dimension, cm	4.7 (4.1; 4.9)	4.5 (4.1; 5.0)	0.0 (–0.3; 0.2)	0.63
LV end-systolic dimension, cm	2.9 (2.6; 3.2)	2.9 (2.6; 3.3)	0.1 (–0.1; 0.2)	0.57
LV end-diastolic posterior wall, cm	0.7 (0.6; 0.7)	0.7 (0.6; 0.9)	0.03 (–0.0; 0.1)	0.04*
Mitral annulus motion, cm	1.5 (1.4; 1.7)	1.7 (1.5; 1.8)	0.1 (–0.0; 0.2)	0.15
Mitral E wave, m/s	72 (63; 83)	73 (59; 88)	–1.3 (–10.5; 3.4)	0.44
Mitral A wave, m/s	69 (57; 81)	64 (55; 82)	–1.7 (–6.7; 8.5)	0.78
Mitral E/A ratio	1.0 (0.8; 1.1)	0.8 (0.8; 1.1)	–0.0 (–0.1; 0.8)	0.38
Lateral mitral annulus a′ wave. cm/s	11 (10; 14)	13 (11; 15)	0.4 (–0.2; 2.1)	0.06
Septal mitral annulus a′ wave, cm/s	11 (10; 13)	11 (9; 13)	0.1 (–1.3; 1.0)	0.68
Lateral mitral annulus e′ wave, cm/s	10 (9; 13)	10 (8; 12)	–0.8 (–1.5; 0.1)	0.11
Septal mitral annulus e′ wave, cm/s	9 (8; 10)	8 (6; 9)	–1.8 (–2.2; –1.0)	0.0004*
Average mitral annulus e′ wave, cm/s	10 (9; 11)	9 (7; 11)	–1.4 (–2.0; –0.2)	0.003*
Lateral E/e′ ratio	6.5 (5.0; 7.6)	6.5 (4.6; 9.5)	–0.1 (–1.0; 1.8)	0.38
Septal E/e′ ratio	7.1 (6.3; 8.1)	8.0 (6.7; 12.2)	1.4 (–0.0; 2.9)	0.01*
Lateral e′/a′ ratio	0.9 (0.7; 1.2)	0.7 (0.6; 0.9)	–0.1 (–0.2; –0.1)	0.002*
Septal e′/a′ ratio	0.8 (0.7; 1.0)	0.7 (0.6; 0.9)	–0.1 (–0.3; 0.0)	0.01*
Patients with diastolic dysfunction	9 (24)	20 (54)		0.02*
Left atrial diameter, cm	3.6 (3.0; 4.0)	3.4 (3.0; 3.9)	0.0 (–0.3; 0.4)	0.44
Left atrial volume index, mL/m^2	21 (17; 27)	20 (16; 26)	–0.7 (–2.8; 3.0)	0.92
Pulmonary artery wedge pressure, mm Hg	10 (9; 12)	11 (9; 15)	0.3 (–0.3; 2.7)	0.11

Data are displayed as median (quartiles) or n (%). LV, left ventricular. * $p < 0.05$.

subjects [28]. Thus, the measured reduction in EF in our COPD collective seems to be noteworthy. In addition, diastolic dysfunction seemed to increase with exposure to higher altitude.

On PW tissue Doppler imaging of the mitral annulus, especially the septal E/e′ ratio increased with altitude, which may suggest a slightly increased LV filling pressure, even though the estimated PAWP and indexed LA volume were unchanged. In healthy individuals, previous studies have shown significant changes in E/A ratio during sojourns to high altitude [25, 28, 35, 36]. Gibbs [37] postulated that impaired diastolic LV filling at altitude is a consequence of an RV pressure overload causing impaired RV function, a reduction of the stroke volume, and thus venous return to the LA. However, Bernheim et al. [38] could not detect any correlation between LV diastolic dysfunction and acute changes in PAP due to exercise and exposure to high altitude in healthy subjects. It remains unclear if increases in PAP may be attributed to diastolic dysfunction or vice versa. The previously mentioned study by Güvenç et al. [31] found no significant difference in mitral E or A wave between patients with COPD living at sea level and those living at moderate altitude (1,768 m). A partial influence of impaired LV diastolic function on increases in PAP cannot be completely dismissed, even though an association was not found in our regression analysis. It remains unclear whether LV systolic and diastolic dysfunction at altitude can be attributed to underlying cardiovascular diseases or whether it is the cause or the consequence of the increased PAP. In this COPD collective with prevalent comorbidities, it is conceivable that coronary heart disease and systemic arterial hypertension contributed to LV dysfunction during the exposure to altitude in some of the patients, but further studies are needed to clarify these assumptions.

Table 4. Linear regression analysis of predictors of the TPG at 2,590 m

Dependent variable: TPG at 2,590 m (mm Hg)	Univariate			Multivariate		
	coefficient	95% CI	*p*	coefficient	95% CI	*p*
Age (years)	–0.5	–1.3 to 0.4	0.324	0.05	–0.6 to 0.7	0.884
Gender	–5.9	–14.8 to 2.9	0.179	–7.8	–15.9 to 0.2	0.056
BMI	0.5	–0.6 to 1.5	0.369			
FEV_1 (% predicted)	–30.0	–69.4 to 9.4	0.130			
SpO_2 peak 6MWD (%)	–0.8	–1.8 to 0.3	0.143			
DLCO (Hb) (% predicted)	–0.15	–0.5 to 0.2	0.360			
TPG at 490 m (mm Hg)	0.7	–0.01 to 1.5	0.054	0.8	0.1 to 1.5	0.029
Ejection fraction (%)	–0.04	–0.07 to 0.6	0.892			
Diastolic dysfunction	0.1	–7.9 to 8.1	0.982			
Blood pressure – systolic (mm Hg)	–0.1	–0.3 to 0.1	0.138			
Heart rate (bpm)	0.1	–0.2 to 0.5	0.411			
aHTN/CVD	6.1	–1.9 to 14.1	0.129			
SpO_2 (%)	0.9	–1.8 to 3.5	0.508			
PaO_2 (kPa)	–0.6	–2.7 to 1.6	0.602			

For all independent variables, baseline measurements at 490 m were included into the analysis. R^2 = 0.315 and p = 0.07 for multivariate regression. TPG, transtricuspid pressure gradient; BMI, body mass index; SpO_2, oxygen saturation; 6MWD, 6-min walking distance; DLCO (Hb), diffusing capacity for carbon monoxide (adjusted for hemoglobin); aHTN, arterial hypertension; CVD, cardiovascular disease; PaO_2, oxygen partial pressure in arterial blood.

Whether the increase in PAP and the deterioration in RV function in lowlanders with COPD is sustained during prolonged exposure to altitude and associated with clinically relevant altitude-related adverse health effects, or whether acclimatization will improve the acute deterioration, is not known. Güvenç et al. [31] have shown a significantly higher PAP in high-altitude residents with COPD, and additionally it has been shown that COPD is associated with higher mortality among inhabitants of higher altitudes compared to lowlanders; however, the underlying mechanism is not yet understood [5, 6]. It might be postulated that the impairment of pulmonary vascular and RV function is one possible explanation.

Limitations

The accuracy of echocardiography in assessing cardiac function depends on acoustic windows; thus, it can be difficult to acquire data of sufficient quality from patients with COPD and emphysema. In our cohort, the echo quality was sufficient to assess predefined parameters in the vast majority of patients, i.e., the TPG could be estimated in 32 (low altitude) and 35 (high altitude) of the 37 participants. Estimates of sPAP, although highly reliable [39], can be under- or overestimated when tricuspid regurgitation is minimal, and thus right heart catheterization would be the investigation of choice; however, this procedure was not feasible for this patient population due to its invasive nature and logistic constraints. The randomized crossover design and blinded double check of stored echocardiographic images were used to limit measurement and sequence biases to the greatest possible extent.

In all, 139 COPD patients from different pulmonology ambulatories throughout Switzerland contacted via telephone refused to participate in this study, mainly due to logistical reasons (subjectively long travel distances and no time to spend 2 nights at altitude and 1 in Zurich). A possible bias can neither be excluded nor derived from those refusals. Furthermore, only patients with COPD GOLD grade 2 or 3 with preserved functional capacity and mild hypoxemia were accepted into the study; therefore, we are not able to comment on any pulmonary vascular changes and the cardiac function of patients with very severe COPD and worse functional capacities, and at higher altitudes than 2,590 m.

Conclusion

This is the first study assessing pulmonary hemodynamics along with RV and LV function in lowlanders with COPD GOLD grade 2 or 3 after 1 night at an altitude of 2,590 m. Hypobaric hypoxia was associated with an increase in PAP comparable to that reported for healthy subjects at much higher altitude, i.e., >4,500 m. Moreover, the COPD patients, some of them with treated hypertension and/or stable cardiovascular disease, displayed an increase in systemic systolic blood pressure, a very slight reduction in LVEF, and potential signs of diastolic dysfunction. Despite these cardiovascular impairments, the patients tolerated the exposure to altitude well, and none of the participants had to descend to lower altitude due to symptomatic altitude-related disease.

Statement of Ethics

The participants gave written informed consent, and the protocol was approved by the Cantonal Ethics Review Board, Zurich, Switzerland.

Disclosure Statement

M.L., K.E.B., M.F., T.D.L., S.M.-M., S.K., and F.T. have no conflict of interest related to this study. S.U. received grants from the Swiss National Science Foundation and the Zurich Lung League and received travel support and speaking fees from Actelion SA, Switzerland, and Bayer SA, Germany. E.G. has received fees for lectures and/or consultations from Actelion, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, United Therapeutics, and Pfizer.

Funding Sources

This work was supported by grants from the Swiss National Science Foundation and the Zurich Lung League.

Author Contributions

M.L. contributed to data acquisition, analysis, and interpretation and drafting of the manuscript. K.E.B., T.D.L., M.F., and S.U. contributed to the conception and design of the study, data acquisition, analysis, and interpretation, and drafting and critical revision of the manuscript, and they approved the final version to be published. E.G., F.T., S.M.-M., and S.K. contributed to data analysis and critical revision of the manuscript and provided final approval of the version to be published.

S.U. has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1 Kelly PT, Swanney MP, Stanton JD, Frampton C, Peters MJ, Beckert LE: Resting and exercise response to altitude in patients with chronic obstructive pulmonary disease. Aviat Space Environ Med 2009;80:102–107.
2 Bijl D, Speelberg B, Folgering HTM: Pulmonary rehabilitation at moderate altitude: a 1-year follow-up. Neth J Med 1994;45:154–161.
3 Karrer W, Schmid T, Wüthrich O, Baldi W, Gall E, Portmann HR: Respiration of patients with chronic lung disease at 500 and 1,500 meter above sea level (in German). Schweiz Med Wochenschr 1990;120:1584–1589.
4 Graham WGB, Houston CS: Short-term adaptation to moderate altitude. Patients with chronic obstructive pulmonary disease. JAMA 1978;240:1491–1494.
5 Burtscher M: Effects of living at higher altitudes on mortality: a narrative review. Aging Dis 2014;5:274–280.
6 Ezzati M, Horwitz ME, Thomas DS, Friedman AB, Roach R, Clark T, Murray CJ, Honigman B: Altitude, life expectancy and mortality from ischaemic heart disease, stroke, COPD and cancers: national population-based analysis of US counties. J Epidemiol Community Health 2012;66:e17.
7 GOLD: GOLD 2017: Global Strategy for the Diagnosis, Management and Prevention of COPD. https://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/.
8 Ulrich S, Hersberger M, Fischler M, Nussbaumer-Ochsner Y, Treder U, Russi EW, Speich R: Genetic polymorphisms of the serotonin transporter, but not the 2a receptor or nitric oxide synthetase, are associated with pulmonary hypertension in chronic obstructive pulmonary disease. Respiration 2010;79:288–295.
9 Chaouat A, Minai OA: Pulmonary hypertension in patients with COPD. Eur Respir Monogr 2012;57:138–147.
10 Kubota Y, Asai K, Murai K, Tsukada YT, Hayashi H, Saito Y, Azuma A, Gemma A, Shimizu W: COPD advances in left ventricular diastolic dysfunction. Int J Chron Obstruct Pulmon Dis 2016;11:649–655.
11 Seeger W, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galiè N, Ghio S, Gibbs S, Martinez FJ, Semigran MJ, Simonneau G, Wells AU, Vachiéry JL: Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol 2013;62(suppl):D109–D116.
12 Fossati L, Müller-Mottet S, Hasler E, Speich R, Bloch KE, Huber LC, Ulrich Somaini S: Long-term effect of vasodilator therapy in pulmonary hypertension due to COPD: a retrospective analysis. Lung 2014;192:987–995.
13 Latshang TD, Furian M, Flück D, Segitz SD, Murer C, Scheiwiller P, Müller-Mottet S, Osmonov B, Küest SM, Steiner A, Ulrich S, Rothe T, Hartmann SE, Poulin MJ, Kohler M, Bloch KE: Effect of travelling to 2,590 m on 6-minute walk distance, blood gases and symptoms of acute mountain sickness in COPD patients (abstract). Respiration 2014;87:522.
14 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories: ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–117.
15 Evangelista A, Flachskampf F, Lancellotti P, Badano L, Aguilar R, Monaghan M, Zamorano J, Nihoyannopoulos P; European Association of Echocardiography: European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. Eur J Echocardiogr 2008;9:438–448.

16 Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU: Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–270.
17 Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB: Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713; quiz 786–788.
18 Kitabatake A, Inoue M, Asao M, Masuyama T, Tanouchi J, Morita T, Mishima M, Uematsu M, Shimazu T, Hori M, Abe H: Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. Circulation 1983;68:302–309.
19 Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA: Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–1533.
20 Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A: Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107–133.
21 Kriemler S, Jansen C, Linka A, Kessel-Schaefer A, Zehnder M, Schürmann T, Kohler M, Bloch K, Brunner-La Rocca HP: Higher pulmonary artery pressure in children than in adults upon fast ascent to high altitude. Eur Respir J 2008;32:664–669.
22 Naeije R, Huez S, Lamotte M, Retailleau K, Neupane S, Abramowicz D, Faoro V: Pulmonary artery pressure limits exercise capacity at high altitude. Eur Respir J 2010;36:1049–1055.
23 Reichenberger F, Kohstall MG, Seeger T, Olschewski H, Grimminger F, Seeger W, Ghofrani HA: Effect of sildenafil on hypoxia-induced changes in pulmonary circulation and right ventricular function. Respir Physiol Neurobiol 2007;159:196–201.
24 Grünig E, Mereles D, Hildebrandt W, Swenson ER, Kübler W, Kuecherer H, Bärtsch P: Stress Doppler echocardiography for identification of susceptibility to high altitude pulmonary edema. J Am Coll Cardiol 2000;35:980–987.
25 Boussuges A, Molenat F, Burnet H, Cauchy E, Gardette B, Sainty JM, Jammes Y, Richalet JP: Operation Everest III (Comex ‘97): modifications of cardiac function secondary to altitude-induced hypoxia. An echocardiographic and Doppler study. Am J Respir Crit Care Med 2000;161:264–270.
26 Modesti PA, Vanni S, Morabito M, Modesti A, Marchetta M, Gamberi T, Sofi F, Savia G, Mancia G, Gensini GF, Parati G: Role of endothelin-1 in exposure to high altitude: Acute Mountain Sickness and Endothelin-1 (ACME-1) study. Circulation 2006;114:1410–1416.
27 Ricart A, Maristany J, Fort N, Leal C, Pagés T, Viscor G: Effects of sildenafil on the human response to acute hypoxia and exercise. High Alt Med Biol 2005;6:43–49.
28 Huez S, Faoro V, Guénard H, Martinot JB, Naeije R: Echocardiographic and tissue Doppler imaging of cardiac adaptation to high altitude in native highlanders versus acclimatized lowlanders. Am J Cardiol 2009;103:1605–1609.
29 Groth A, Saxer S, Bader PR, Lichtblau M, Furian M, Schneider SR, Schwarz EI, Bloch KE, Ulrich S: Acute hemodynamic changes by breathing hypoxic and hyperoxic gas mixtures in pulmonary arterial and chronic thromboembolic pulmonary hypertension. Int J Cardiol DOI: 10.1016/j.ijcard.2018.05.127.
30 Furian M, Hartmann SE, Latshang TD, Flück D, Murer C, Scheiwiller PM, Osmonov B, Ulrich S, Kohler M, Poulin MJ, Bloch KE: Exercise performance of lowlanders with COPD at 2,590 m: data from a randomized trial. Respiration 2018;95:422–432.
31 Güvenç TS, Erer HB, Kul S, Perinçek G, Ilhan S, Sayar N, Yıldırım BZ, Doğan C, Karabağ Y, Balcı B, Eren M: Right ventricular morphology and function in chronic obstructive pulmonary disease patients living at high altitude. Heart Lung Circ 2013;22:31–37.
32 Bartsch P, Gibbs JS: Effect of altitude on the heart and the lungs. Circulation 2007;116:2191–2202.
33 Otterstad JE, Froeland G, St John Sutton M, Holme I: Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. Eur Heart J 1997;18:507–513.
34 Rao M, Li J, Qin J, Zhang J, Gao X, Yu S, Yu J, Chen G, Xu B, Li H, Rao R, Huang L, Jin J: Left ventricular function during acute high-altitude exposure in a large group of healthy young Chinese men. PLoS One 2015;10:e0116936.
35 Allemann Y, Rotter M, Hutter D, Lipp E, Sartori C, Scherrer U, Seiler C: Impact of acute hypoxic pulmonary hypertension on LV diastolic function in healthy mountaineers at high altitude. Am J Physiol Heart Circ Physiol 2004;286:H856–H862.
36 Stembridge M, Ainslie PN, Hughes MG, Stöhr EJ, Cotter JD, Nio AQ, Shave R: Ventricular structure, function, and mechanics at high altitude: chronic remodeling in Sherpa vs short-term lowlander adaptation. J Appl Physiol (1985) 2014;117:334–343.
37 Gibbs JS: Biventricular function at high altitude: implications for regulation of stroke volume in chronic hypoxia. Adv Exp Med Biol 2007;618:13–24.
38 Bernheim AM, Kiencke S, Fischler M, Dorschner L, Debrunner J, Mairbäurl H, Maggiorini M, Brunner-La Rocca HP: Acute changes in pulmonary artery pressures due to exercise and exposure to high altitude do not cause left ventricular diastolic dysfunction. Chest 2007;132:380–387.
39 Greiner S, Jud A, Aurich M, Hess A, Hilbel T, Hardt S, Katus HA, Mereles D: Reliability of noninvasive assessment of systolic pulmonary artery pressure by Doppler echocardiography compared to right heart catheterization: analysis in a large patient population. J Am Heart Assoc 2014;3:e001103.